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Case Report

Neuromyelitis optica and liver cirrhosis: an association or co-incidence

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ABSTRACT

Neuromyelitis optica (NMO) is a rare central nervous system demyelination syndrome predominantly targeting optic nerves and the spinal cord. Here we present a middle-aged female presenting with new onset quadriparesis and a history of persistent splenomegaly and pancytopenia, eventually being diagnosed as NMO along with autoimmune cirrhosis. The association of NMO spectrum disorders (NMOSD) with chronic liver disease has not been previously described in the literature. The purpose of this case report is to bring forward an unusual presentation and to ascertain whether it could be part of a heterogenous spectrum of an autoimmune disorder, or merely a co-incidence.

Keywords: NMO, Cirrhosis, Quadriparesis

INTRODUCTION

Neuromyelitis Optica (NMO), also known as Devic's disease, is an inflammatory disorder characterised by recurrent attacks of optic neuritis and myelitis.[1] The pathophysiology of NMO is inflammation, loss of astrocytes and an absence of staining of the water channel protein AQP4 by immunohistochemistry with demyelination and deposition of antibody along with complement.[2] A variety of immune mediated disorders like Sjogren's syndrome, systemic lupus erythematosus, CNS vasculitis and other organ limited specific autoimmune disorders have been recently linked to NMOSD, though robust evidence regarding their prevalence remains scarce.[3]

Cirrhosis consists of development of fibrosis of liver leading to distortion of parenchymal architecture along with the formation of regenerative nodules resulting in a decrease in hepatocellular mass and function along with alteration of blood flow.[4] Several metabolic, infectious, and environmental factors may determine the development of liver cirrhosis in an individual. Immune dysregulation is an uncommon cause of liver cirrhosis and may be associated with other autoimmune disorders including disorders of CNS demyelination.[5]

Comprehensive literature on the association of liver disease and NMO is scarce. Here we present a middle-aged female presenting with new onset quadriparesis and a history of persistent splenomegaly and pancytopenia, eventually being diagnosed as NMO along with autoimmune cirrhosis.

CASE REPORT

A middle-aged female, resident of North India, with no known comorbidities or addictions presented to the emergency department with history of weakness in all limbs, 3 weeks prior to hospital admission. The weakness was gradual in onset, starting from both lower limbs simultaneously and then gradually involving both upper limbs over a span of 10 days. The patient explained it as a feeling of stiffness initially with inability to walk, followed by a bedridden state in 10 days and inability to turn around in the bed in next 7 days. She also noticed decreased sensation in both the lower limbs and an episode of burn injury at feet without her notice in initial days of onset of illness. She recalls having a similar

illness episode 1 year back when she was treated with oral steroids and recovered in a span of 2 weeks. History was significant for multiple blood transfusions and a diagnosis of 'persistent splenomegaly' since the last 3 years. She had also developed abdominal distension in the past 4 weeks which had progressed till the time of admission. There was no complaint of jaundice, bleeding from any orifice or black coloured stools. No other history of surgery, allergies, recreational drugs, over the counter medications, alcohol, tobacco abuse or herbal medication intake was present. There was no history of recent vaccinations. The family history was unremarkable.

On physical examination, the blood pressure was 128/80 mm Hg, heart rate 100 bpm, respiratory rate 20 breaths/min, body temperature 36.9 C, saturation of oxygen 99% on room air and the patient's body mass index 21.5 kg/m^2. The Glasgow Coma score was 15/15 and MMSE was scored 30/30. Ophthalmological examination revealed a positive swinging flashlight test with right sided relative afferent pupillary defect (RAPD). Other cranial nerves were examination revealed no abnormality. Nervous system examination revealed hypertonia with exaggerated reflexes and positive bilateral Babinski. Power of muscles of upper limb was 3/5 bilaterally and 1/5 bilaterally in lower limbs.

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Investigations showed pancytopenia, ALT/AST-48 U/l/60U/l, Serum Creatinine 0.29 mg/dl, negative HIV rapid test, HCV antibody and HBsAg antigen. Thyroid function test, blood sugar, electrolytes were within normal limits. Ascitic fluid examination revealed high serum ascites albumin gradient (SAAG) and low protein with 150 cells predominantly polymorphs. Ultrasound abdomen revealed chronic liver disease with increased portal vein diameter and splenomegaly. Visual evoked potential showed prolonged P100 latency on both sides. Cerebrospinal fluid (CSF) study revealed an opening pressure of 25 cm of water and clear fluid with normal cell count, protein, and glucose. CSF culture showed no bacterial growth and was negative for oligoclonal bands. IgG antibody for aquaporin 4 was strongly positive. Chest X-ray and electrocardiography were normal. MRI brain was indicative of patchy short segment hyper intensities with enhancement involving cervical and dorsal spine from C2 to D7, periventricular white matter lesions and right optic nerve atrophy (Figure 1 and 2).

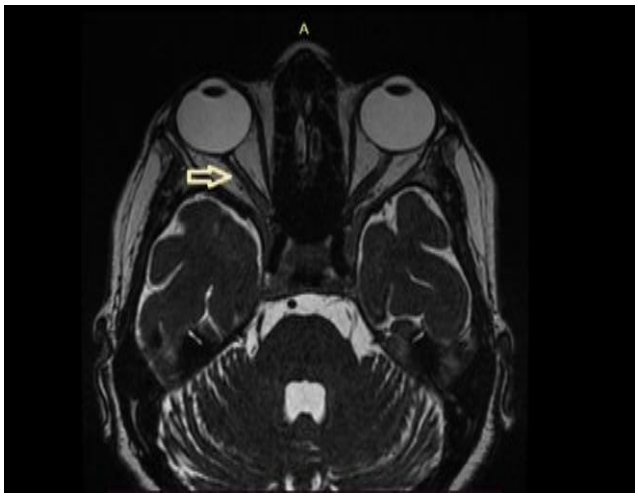

Figure 1: T2 axial section showing reduced bulk of the right optic nerve (arrow) as compared to left optic nerve, suggestive of right optic nerve atrophy.

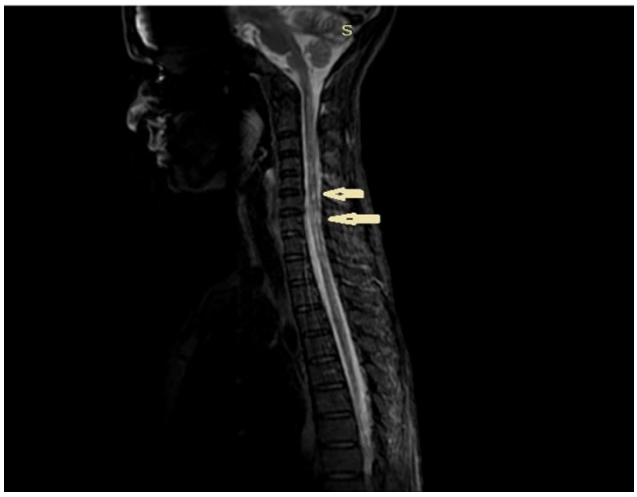

Figure 2: Sagittal STIR image showing patchy areas of hyperintensities in the cervical and dorsal cord (arrows).

Serum ceruloplasmin levels were sent which were reported to be within normal limits and slit lamp examination was negative for Kayser Fleischer rings. Autoimmune workup was sent and came out to be positive for ANA (1:160 titre), SMA (1:80 titre) and negative for LKM, or SLA antibodies. IgG was higher than the upper limit of normal and viral markers including Hepatitis C and B were negative. Hence a diagnosis of probable autoimmune chronic liver disease was made. The patient was counselled for liver biopsy but was deferred by the patient due to financial constraints.

Before the initiation of steroid therapy, upper gastrointestinal endoscopy was performed to rule out

oesophageal varices. The patient was started on pulse corticosteroid therapy for three days followed by oral corticosteroids with gradual tapering Improvement was assessed through daily charting of muscle power. Power of muscles of upper limbs was 5/5 bilaterally in upper limbs and 4/5 bilaterally in lower limbs on discharge following the steroid course, thus confirming the diagnosis of NMO. The patient was asked to follow up for screening for HCC at six-month interval and with upper gastrointestinal endoscopy at a 3 yearly interval for oesophageal varices.

DISCUSSION

NMO is a demyelinating disorder of the central nervous system whereas liver dysfunction may be associated in patients of NMO, not due to the disease itself, but via several other factors like drug toxicity, fatty infiltration, and viral infection.[6] In our case, the development of liver disease along with its complications, pre-dated the development of autoimmune features hence drug toxicity or concurrent viral infection was unlikely.

A few cases have been reported providing an association between NMO and autoimmune hepatitis.[7] Autoantibodies against the glycolytic enzyme phosphoglycerate mutase 1 (PGAM1), have been proposed as a diagnostic marker for AIH.[8] The same PGAM1 autoantibodies are in a higher proportion of patients affected by autoimmune neurologic diseases, particularly MS and NMO concerning those with other neurologic diseases and healthy controls.[9] A single case study also reported the occurrence of NMO induced by the administration of interferon-alpha.[10] Several autoimmune inflammatory etiologies may similarly affect the central nervous system, such as Sjogren's syndrome and primary biliary cirrhosis, thus the presence of liver disease and demyelination in our case could reflect different manifestations of a heterogeneous syndrome.[11] A likely explanation of this association would be an autoimmune hepatitis-induced chronic liver disease which pre-dated the neurological manifestations in this case. Up to 30% of autoimmune hepatitis has been reported to be seronegative with a definitive diagnosis possible only with biopsy.[12] The most common clinical phenotype of autoimmune hepatitis (two-thirds of patients) is characterized by an insidious onset with nonspecific symptoms such as fatigue, malaise, and weight loss; one-third of the patients at diagnosis have already developed cirrhosis irrespective of the presence of symptoms due to the delay in diagnosis.[13] In this case, the patient had similar symptoms of fatigue, weight loss, and a 'persistent splenomegaly' with left upper quadrant fullness for three years, suggesting that she developed liver disease with cirrhosis and splenomegaly much before the initial presentation.

B cells play a significant in the pathogenesis of NMOSD through the production of specific AQP4 antibodies and the development of follicular effector T cells, which participate in B cell differentiation and isotype switching; along with increased production of B cell cytokines promoting NMOSD activity, including IL-6 and TNF-alpha.[14] Evidence also indicates that AQP4-Ab are synthesized peripherally, rather than intrathecally, subsequently entering the CNS through a disrupted blood-brain barrier.[15] Similar cytokines and specific antibody-mediated injury are also responsible for hepatocyte injury and disease progression in autoimmune liver disease. A similar overlap has been studied for multiple sclerosis, a similar autoimmune CNS demyelinating disorder. In a biochemical analysis by Tsouris et al 30 patients out of 133 with multiple sclerosis had antibody positivity for autoimmune hepatitis.[16] Sayin et al reported a similar association between histologically proven autoimmune liver injury and multiple sclerosis in a case series of 3 cases.[17] One of the limitations of the case was the absence of a liver biopsy which could have confirmed the hypothesis of a possible autoimmune nature of the liver injury.

However, ours is a unique case ruling out all the infective, metabolic and toxin-related causes of cirrhosis and with laboratory parameters suggesting autoimmune hepatitis, leaving us with the diagnostic dilemma - whether the patient is afflicted with two separate diseases or one causing the other- an actual association between the usually nonrelated diseases or a mere coincidence.

CONCLUSION

NMO is a rare central nervous system demyelinating disorder and has been associated with various autoimmune disorders. However, its association with liver cirrhosis has been rarely reported. In the above scenario infective, metabolic, toxin related causes of cirrhosis were ruled out. Hence whether the presence of probable autoimmune cirrhosis and CNS demyelination in the same patient was a part of a single disease pathophysiology or a mere coincidence will need further research on similar presentations.

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